comprises a dimeric scF_v molecule.

46. (Amended) An antibody or antibody fragment according to claim 30, which comprises CGS-1 or CGS-2.

47. (Amended) A pharmaceutical composition comprising an antibody or antibody fragment according to claim 30, in an effective amount for binding thereof to a fibronectin ED-B–containing cell, and a pharmaceutically-acceptable excipient.

53. (Amended) A diagnostic kit comprising an antibody or antibody fragment according to claim 30 and one or more reagents that allow the determination of the binding of said antibody or antibody fragment to a cell.

54. (Amended) An antibody or antibody fragment of claim 30, which is isolated from a synthetic molecular library.

55. (Amended) An antibody or antibody fragment of claim 30, which is not naturally occurring.

56. (Amended) An antibody or antibody fragment of claim 30, in isolated form.

57. (Amended) An antibody of claim 30.

REMARKS

Appreciation is expressed to the Examiner for a series of telecons which have explained various features of the Office Action and, it is believed, led to the expeditious resolution of issues.

The Examiner notes some apparent confusion in the relationship of the claims of this application to the prior art. This was derived from the language of claim 34. The Examiner has questioned whether this language could lead to a claim interpretation which would read on the prior art antibody BC-1. For the following reasons, it can be seen that there is no such problem.

The subject language states that fibronectin (FN) contains "type III homology repeats which include the ED-B domain." This language is in fact correct. As stated in the application, e.g., on page 4, lines 13-14:

> The ED-B sequence is a complete type III-homology repeat encoded by a single exon and comprising 91 amino acids.

Moreover, note the disclosure at page 4, lines 19-27:

> The presence of B+ isoform itself constitutes a tumour-induced neoantigen, but in addition, ED-B expression exposes a normally cryptic antigen within the type III repeat 7 (preceding ED-B); since this epitope is not exposed in FN molecules lacking ED-B, it follows that ED-B expression induces the expression of neoantigens both directly and indirectly. This cryptic antigenic site forms the target of a monoclonal antibody (mAb) named BC-1 (Carnemolla et al, 1992).

In other words, it is true that the ED-B domain is a type III-homology repeat. However, it is established in the prior art that the known antibody BC-1 is specific to an epitope in homology repeat number 7, which is a homology repeat different form that comprising the ED-B sequence.

Another copy of the Carnemolla 1992 paper is attached. It confirms the two quoted passages from the specification:

> The ED-B oncofetal domain, a complete type III homology repeat composed of 91 amino acids and coded for by a single exon, is the most conserved FN region with 100% and 96% homology with rat and chicken FN, respectively (Norton and Hynes, 1987); Zardi et al., 1987) [sic].

> Given this specificity, we assumed that the epitope recognized by the mAb BC-1 was localized within the ED-B sequence (Carnemolla at al., 1989). However, we now demonstrate that this eptiope is localized within the type III repeat 7 (which precedes the ED-B) and that it is cryptic in FN molecules lacking the ED-B, while it is unmasked in molecules containing this sequence.

Although it was once thought that BC-1 was specific for the ED-B domain, Carnemolla et al. have established that this was mistaken. In fact, the prior art antibody is specific for the type III homology repeat 7 and not the B-domain which is in a different type III-repeat of FN, i.e., the one following repeat 7.

Hopefully, this explanation will alleviate whatever confusion there was. As can be seen, all the prior art rejections should be withdrawn.

The recommendations made by the Examiner in paragraphs 14, 15 and 18 have been adopted. Appreciation is expressed.

It is believed that the Examiner has agreed in the mentioned telecons that the current claims are clearly enabled in the scope of the term "antibody or antibody fragment," which is part of the preamble and which, in the context of this application and claims, is clearly a limiting feature. As explained in the specification, prior to this invention, skilled workers who had labored for many years on the problem, had not been able to prepare antibodies which were directly binding to the ED-B domain of fibronectin. Possible reasons for this are discussed in the background section of the specification. The inventors solved the problem by utilizing a phage-display technique which surprisingly avoided the defects of the prior art and led to the first preparation of antibodies directly binding to the ED-B domain. With this achievement and in view of the information, data and guidance of this specification, a skilled worker could prepare antibodies and antibody fragments readily, using conventional technology, as the examiner notes on page 6, last three lines. Thus, the current version of the claims is clearly enabled. This is not to imply that the prior version of the claims was not enabled. Applicants are currently contemplating the filing of a continuation application to pursue subject matter deleted from this application.

As the Examiner notes, one of the uses for the antibodies and fragments of this invention is for implementation in therapy. Other uses are discussed on pages 13-17 of the application,

including diagnostics, e.g., of tumors, etc. The Examiner seems to be implying that proof of the asserted utilities is needed for patentability of claim 47. However under clear, longstanding law, such proof is not necessary unless the PTO has provided reasons or evidence to doubt the presumptive accuracy of a patent specification's disclosure of utility. *In re Marzocchi.* 439 F. 2d 220, 169 USPQ 367 (CCPA 1971). Furthermore, in the pharmaceutical field, the Federal Circuit has made clear that early stage disclosures are encouraged and that proof of utility is rarely needed. See, e.g., *In re Brana*, 51 F. 3d 1560, 34 USPQ 2d 1436 (Fed. Cir. 1995). The lack of proof of the asserted therapeutic utility in no way is a defect of a patent application. The burden is not shifted to applicant to prove the asserted utility.

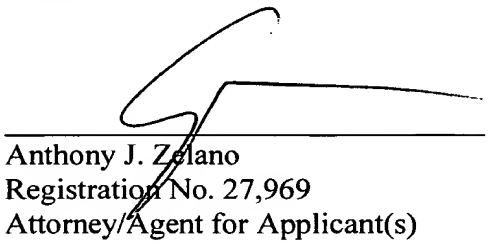
Moreover, the examiner appears to agree that that diagnostic uses are enabled. But a compound or composition need have only one disclosed and enabled use. Thus, even if therapeutic uses were not enabled (not the case), the pharmaceutical composition claim would satisfy all requirements of 35 U.S.C. 101 and 112 in view of this single use.

In any event, the therapeutic uses are enabled by the details given in the specification, and especially in combination with well known conventional considerations employed in the several antibodies already approved by FDA for treatment of various diseases and/or which are in ongoing clinical trials. This kind of technology is not in any way incredible. This establishes the "precedent" mentioned by the examiner on page 8, lines 4-6 of the office action. The claimed "pharmaceutical" composition has a credible utility and is fully enabled.

Furthermore, although not necessary at all, in an effort to further expedite prosecution, applicants submit non-prior-art Nilsson et al. (including coinventors), Cancer Research 61, 711-716, January 15, 2001, and Santimaria et al. (including coinventors), Clinical Cancer Research, Vol. 9, 571-579, February 2003. These provide the type of data the examiner mentions in lines 4-6 of page 8 of the office action for a species within the current claims.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Attorney Docket No. :NOTAR-2

Date: April 10, 2003

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Page 20, before line 11, insert the following title: --BRIEF DESCRITPION OF THE DRAWINGS--.

Please amend the application as follows:

30. (Amended) An antibody or antibody fragment ~~A specific binding member~~ which is specific for and binds directly to the ED-B oncofoetal domain of fibronectin (FN).

31. (Amended) An antibody or antibody fragment according to ~~A specific binding member to~~ claim 30, which comprises a mammalian ~~an~~ antibody-antigen binding domain.

32. (Amended) An antibody or antibody fragment according to claim 31, ~~A specific binding member according to claim 31~~, wherein said antibody-antigen binding domain is of human origin.

33. (Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, which binds to FN containing ED-B after treatment of the FN with the protease thermolysin.

34. (Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, which binds to recombinant FN containing type III homology repeats which include the ED-B domain.

35. (Amended) An antibody or antibody fragment ~~A specific binding member~~

according to claim 30, whose binding to B-FN is inhibited by the ED-B domain.

36. (Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, which binds to B-FN from human, mouse, rat, chicken, and any other species in which the ED-B domain is conserved.

37. (Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, which binds to B-FN without treatment of the FN with N-glycanase.

38. (Twice Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, having a variable heavy (VH) chain region of the sequence (aa 1 Glu – aa 98 Arg inclusive in Figure 1) (SEQ ID NO: 9) and the CDR3 sequence Ser Leu Pro Lys (SEQ ID NO: 12).

39. (Twice Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, having a variable heavy (VH) chain region of the sequence (aa 1 Glu – aa 98 Arg inclusive in Figure 1) (SEQ ID NO.: 9) and the CDR3 sequence Gly Val Gly Ala Phe Arg Pro Tyr Arg Lys His Glu (SEQ ID NO:1).

40. (Twice Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, having a variable light (VL) chain region of the sequence (au 1 Ser – aa 90 Ser inclusive in Figure 1) (SEQ ID NO.: 10) and the remainder of the CDR3 sequence as Pro Val Val Leu Asn Gly Val Val (SEQ ID NO: 13).

41. (Twice Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, having a variable light (VL) chain region of the sequence (aa 1 Ser – aa 90 Ser inclusive in Figure 1) (SEQ ID NO.: 11) and the remainder of the CDR3 sequence as Pro Phe Glu His Asn Leu Val Val (SEQ ID NO: 14).

42. (Twice Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, having a variable heavy (VH) chain region of the sequence (aa 1 Glu – aa 98 Arg inclusive in Figure 1) (SEQ ID NO.: 9) and the CDR3 sequence.

43. (Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, which, when measured as a purified monomer, has a dissociation constant (K_d) of about 6×10^{-8}M for ED-B FN.

44. (Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, which ~~wherein said binding member~~ comprises an scF_v molecule.

45. (Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, ~~wherein said binding member~~ which comprises a dimeric scF_v molecule.

46. (Amended) An antibody or antibody fragment ~~A specific binding member~~ according to claim 30, ~~wherein said binding member~~ which comprises CGS-1 or CGS-2.

47. (Amended) A pharmaceutical composition comprising an antibody or antibody fragment ~~A specific binding member~~ according to claim 30, in an effective amount for binding thereof to fibronectin ED-B-containing cell, and a pharmaceutically-acceptable excipient.

53. (Amended) A diagnostic kit comprising an antibody or antibody fragment ~~a specific binding member~~ according to claim 30 and one or more reagents that allow the determination of the binding of said antibody or antibody fragment ~~member~~ to a cell.

54. (Amended) An antibody or antibody fragment ~~A specific binding member~~ of claim 30, which is isolated from a synthetic molecular library.

55. (Amended) An antibody or antibody fragment ~~A specific binding member~~ of

claim 30, which is not naturally occurring.

56. (Amended) An antibody or antibody fragment ~~A specific binding member~~ of claim 30, in isolated form.

57. (Amended) An antibody ~~A specific binding member~~ of claim 30, ~~which is an antibody or an antibody fragment~~.